Paper No. 29

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DONALD W. KUFE, and RALPH R. WEICHSELBAUM

Appeal No. 2001-0690
Application No. 08/309,315

ON BRIEF[1]

Before ROBINSON, ADAMS, and MILLS, Administrative Patent Judges.
ADAMS, Administrative Patent Judge.

DECISION ON APPEAL[2]

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 7, 9, 12-14 and 22-24, which are all the claims pending in the application.[3]

[1] Pursuant to appellants request (Paper No. 26, received February 26, 1998) an oral hearing for this appeal was scheduled (Paper No. 27, mailed April 18, 2001) for Tuesday, September 11, 2001. However, we note appellants waived (Paper No. 28, received May 9, 2001) their request for oral hearing. Accordingly, we considered this appeal on Brief.

[2] We note appellants' statement, in Appeal No. 1999-1353 (Application No. 08/520,923), that the instant appeal is related to Appeal No. 1999-1353 and Appeal No. 1999-1475 (Application No. 08/248,058). Accordingly, these appeals were considered together.

[3] Appellants' After Final amendment (Paper No. 20, received 3/19/97), inter alia, cancelled claims 1-6, 10, 11 and 15-21. The examiner's Advisory Action (Paper No. 21, mailed April 7, 1997) approved entry of this amendment. The administrative file, however, does not indicate that these claims were cancelled. Prior to any further action, the examiner should insure that the administrative accurately reflects the correct status of the claims.

Claims 7, 12 and 22 are illustrative of the subject matter on appeal and are reproduced below:

7. A process of increasing cell death comprising the steps of:
(a) treating cells with a DNA damaging agent; and
(b) contacting the cells with a protein tyrosine kinase inhibitor.

12. A method for the treatment of neoplastic disease in a patient comprising the steps of:
(a) administering to the patient a pharmaceutically acceptable preparation which includes a therapeutically effective amount of a tyrosine kinase inhibitor; and
(b) treating neoplastic cells with a therapeutically effective amount of a DNA damaging agent.

22. A method of increasing the effect of ionizing radiation on cell killing, comprising the steps of:
(a) treating the cells with a therapeutically effective amount of ionizing radiation; and
(b) contacting the cells with a protein tyrosine kinase inhibitor.

The references relied upon by the examiner are:

Margolis et al. (Margolis) 5,262,409 Nov. 16, 1993

Uckun et al. (Uckun), "Ionizing radiation stimulates unidentified tyrosine-specific protein kinases in human B-lymphocyte precursors, triggering apoptosis and clonogenic cell death," Proc. Natl. Acad. Sci. USA, Vol. 89, pp. 9005-9009 (1992)

Akinaga et al. (Akinaga), "Enhancement of antitumor activity of mitomycin C in vitro and in vivo by UCN-01, a selective inhibitor of protein kinase C," Cancer Chemother. Pharmacol., Vol. 32, pp. 183-189 (1993)

GROUNDS OF REJECTION

Claims 7, 9 and 12-14 stand rejected under 35 U.S.C. § 103 as being unpatentable over Margolis in view of Akinaga.

Claims 7, 9, 12-14 and 22-24 stand rejected under 35 U.S.C. § 103 as being unpatentable over Uckun.

We reverse.

DISCUSSION

In reaching our decision in this appeal, we considered appellants' specification and claims, in addition to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's Answer[4] for the examiner's reasoning in support of the rejections. We further reference appellants' Brief[5] for the appellants' arguments in favor of patentability.

THE REJECTION UNDER 35 U.S.C. § 103:

Margolis in view of Akinaga

The examiner refers (Answer, page 4) our attention to the statement of the rejection set forth in the Final Rejection[6].

We initially note that in contrast to the examiner's position (Final Rejection, page 3) appellants do not concede (See Brief, pages 10-11) that the use of a tyrosine kinase inhibitor is not critical since the protein kinase inhibitor may be a serine/threonine kinase inhibitor or a tyrosine protein kinase inhibitor. Instead, appellants maintain (Brief, bridging sentence, pages 10-11) "there is no

[4] Paper No. 25, mailed December 23, 1997.
[5] Paper No. 24, received September 15, 1997.
[6] Paper No. 18, mailed December 18, 1996.

basis for concluding that serine/threonine protein kinases would act similarly to tyrosine protein kinases in conjunction with a DNA damaging agent," as claimed.

According to the examiner (Final Rejection, page 3) "Margolis and Akinaga teach killing cells using a DNA damaging agent, combined with a protein kinase inhibitor. Akinaga teaches that kinase inhibitors are routinely used in anti-tumor therapy, i.e., in a treatment whereby cells are killed." Therefore, the examiner concludes "[o]ne would expect a reasonable expectation of success of substituting the specific tyrosine kinase inhibitor claimed for the generic protein kinase inhibitor taught by the references to achieve cell killing based on the fact that the references teach that protein kinase inhibitors in general kill cells."

According to appellants (Brief, page 11) "the teaching of Akinaga is clearly that inhibitors of protein kinase C, a serine/threonine protein kinase, can potentiate the effect of the antitumor agent MMC, but general inhibitors of protein kinases do not have such an effect." Accordingly, appellants argue (Brief, bridging sentence, pages 11-12) that "the practitioner of the art would be led by Akinaga to conclude only that selective inhibitors of serine/threonine protein kinases could potentiate the effects of anti-cancer agents, while general inhibitors of protein kinases, including tyrosine protein kinases would not have such effects."

Appellants further argue (Brief, page 12) "Akinaga [pages 183-184] clearly demonstrates that the state of the art at the time of the instant invention was one of uncertainty with regard to the effects of protein kinase inhibitors on anticancer agents." Accordingly appellants conclude (id.) "there could have been no

reasonable likelihood of success in predicting the combination of tyrosine protein kinase inhibitors with DNA damaging agents."

The examiner does not specifically address appellants' argument. Instead, the examiner argues (Answer, page 4) "[t]he references detail that the inhibition of protein kinases adversely affects the cells' multiplication and growth and in doing so has a synergistic effect when used in combination with DNA damaging agents." We note the examiner's reference to "protein kinases" and not to "protein tyrosine kinases" which is, inter alia, the subject matter of appellants' claimed invention. This distinction is more pronounced in the examiner's argument (id.) that "PTK's [protein tyrosine kinases] (e.g. the Src-family), as with the protein kinases targeted in Margolis and Akinaga, are instrumental in the proliferation of cells" [emphasis added].

Therefore, instead of identifying precisely where his supporting references teach protein tyrosine kinases, the examiner enters into a discussion of the involvement of protein tyrosine kinases in cell proliferation, and attempts to connect this discussion with the teachings of Margolis and Akinaga. However, as appellants point out (Brief, page 11) protein kinase C, the subject matter of Akinaga, is not a protein tyrosine kinase; protein kinase C is a serine/threonine protein kinase. With regard to Margolis, appellants point out (Brief, page 12) that "there is no evidence of record to suggest that … [2-aminopurine and 6-dimethylaminopurine] are tyrosine protein kinase inhibitors."

On this record, the examiner failed to provide the factual evidence necessary to establish a nexus between protein tyrosine kinase inhibitors and

the teachings of Margolis and Akinaga. We remind the examiner "[t]he Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because it may doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis." In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968). In addition, as set forth in In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000):

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. … Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." …
>
> Most if not all inventions arise from a combination of old elements. … Thus, every element of a claimed invention may often be found in the prior art. … However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. … Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. [citations omitted]

In other words, "there still must be evidence that 'a skilled artisan, . . . with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.'" Ecolochem Inc. v. Southern California Edison, 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1075-76 (Fed. Cir. 2000). On this record, the examiner did not provide the factual evidence necessary to establish that absent appellants' disclosure, a person of

ordinary skill in the art would have combined the elements from the cited prior art in a manner that would have resulted in appellants' claimed invention.

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). On these circumstances, it is our opinion that the examiner failed to provide the evidence necessary to support a prima facie case of obviousness. Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Accordingly, we reverse the rejection of claims 7 and 9-14 under 35 U.S.C. § 103 as being unpatentable over Margolis in view of Akinaga.

Uckun

The examiner refers (Answer, page 4) our attention to the statement of the rejection set forth in the Final Rejection. According to the examiner (Final Rejection, page 5):

> Uckun states that the cells were irradiated. Clearly, if cells are irradiated, they are killed. On page 9006, column 1, the phrase "[a]poptosis [a]ssays" is recited. This is further proof that Uckun intended to kill the cells. In addition, on page 9008, column 1, Uckun states that "these findings provide direct evidence that ionizing radiation stimulates PTKs" and that "tyrosine phosphorylation plays an important role in the initiation of apoptosis in human B-lymphocyte precursors exposed to ionizing radiation"….

According to appellants (Brief, page 8) "Uckun teaches that tyrosine phosphorylation plays an important role in the initiation of apoptosis. Apoptosis is a descriptive term for programmed cell death. Thus, according to Uckun, the

initiation of cell death is dependent upon having active tyrosine kinases present in the cell…." Therefore, appellants conclude (id.) that the "entire process [taught by Uckun] would be expected to be reversed by the tyrosine kinase inhibitors that are the subject of the instant invention." We agree.

In response, the examiner argues "there is a myriad of protein tyrosine kinases … with a plurality of functions within the cells. … Uckun discovered that ionizing radiation also had the effect of stimulating unidentified PTK's…. Therefore … it would be obvious to combine a PTK [inhibitor] with radiation…." We cannot agree with the examiner's position.

Uckun clearly teaches (page 9008, column 1, third full paragraph):

> genistein [a claimed protein tyrosine kinase inhibitor, see e.g. appellants' claim 9] prevented … apoptosis-related morphologic changes in irradiated cells, with <25% of cells showing apoptosis-related changes in morphology… providing evidence that tyrosine phosphorylation plays an important role in the initiation of apoptosis in human B-lymphocyte precursors exposed to ionizing radiation.

Accordingly we agree with appellants' argument (Brief, page 8) that "Uckun teaches away from the present invention." We remind the examiner, that in determining whether the claimed invention is obvious, a prior art reference must be read as a whole and consideration must be given where the reference teaches away from the claimed invention. Akzo N.V., Aramide Maatschappij v.o.f. v. United States Int'l Trade Comm'n, 808 F.2d 1471, 1481, 1 USPQ2d 1241, 1246 (Fed. Cir. 1986).

On these circumstances, it is our opinion that the examiner failed to provide the evidence necessary to support a prima facie case of obviousness.

Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. See Fine. Accordingly, we reverse the rejection of claims 7, 9-14 and 22-24 under 35 U.S.C. § 103 as being unpatentable over Uckun.

REVERSED

Douglas W. Robinson Administrative Patent Judge	)
Donald E. Adams Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
Demetra J. Mills Administrative Patent Judge	)

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